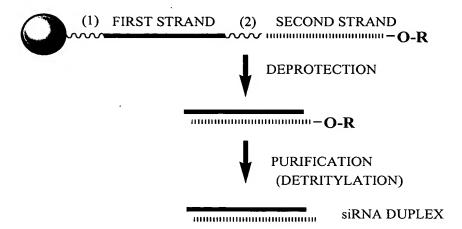
Inventor: McSwiggen et al. Attorney Docket No. 02-742-O (400.144) Sheet 1 of 15

Figure 1



= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

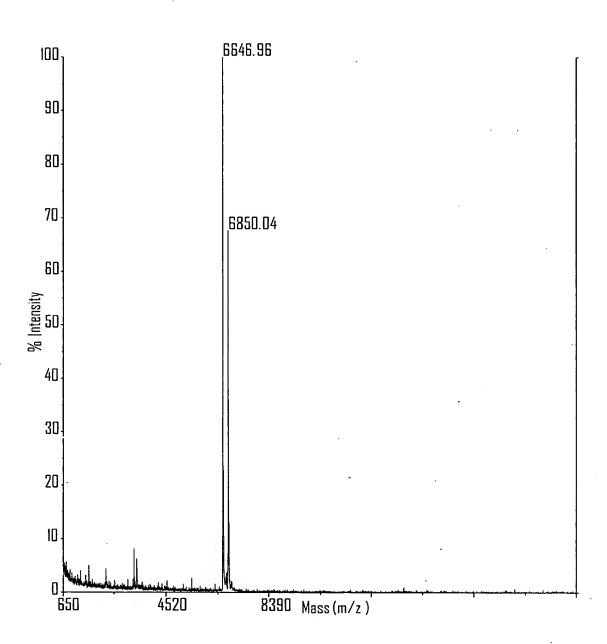
= CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

INVERTED DEOXYABASIC SUCCINATE LINKAGE

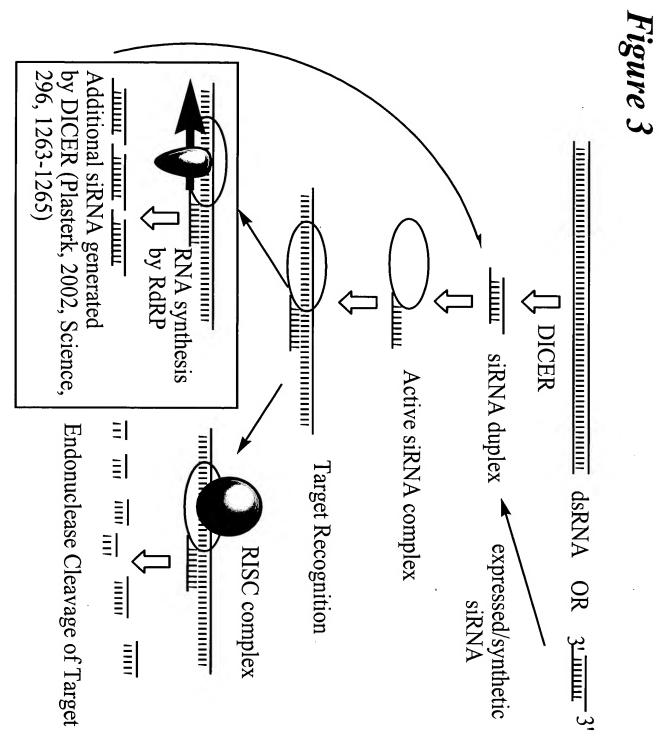
GLYCERYL SUCCINATE LINKAGE

Inventor: McSwiggen et al.
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Figure 2



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Figure 4

A	SENSE STRAND (SEQ ID NO 456) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
	5'- B-NNNNNNNNNNNNNNNNNNNNNNNNN (NN)-B -3	٠
A	$\int 3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	, ۲
	ANTISENSE STRAND (SEQ ID NO 457) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 458) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N)	
_	5'- NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	
B	$\langle 3'$ - L-(N _s N) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	\
	ANTISENSE STRAND (SEQ ID NO 459) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
		Ś
	SENSE STRAND (SEQ ID NO 460) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)	
\boldsymbol{C}	J 5'- B-N N N N N N N N N N N N N N N N N N	٠ ل
	$\int 3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNN -5	' [
	ANTISENSE STRAND (SEQ ID NO 461) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 462) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
D	5'- B-NNNNNNNNNNNNNNNNNNNNNNNNN -3'	
D	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	7
	ANTISENSE STRAND (SEQ ID NO 459) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 463) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N))
E	5'- B-N N N N N N N N N N N N N N N N N N	
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7
	ANTISENSE STRAND (SEQ ID NO 459) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 462))
	ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
F	5'- B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	}
	$3'$ - L- (N_sN) N N N N N N N N N N N N N N N N N N	
	ANTISENSE STRAND (SEQ ID NO 464) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
		-

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY REPORTED.

L = GLYCERYL or B THAT IS OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

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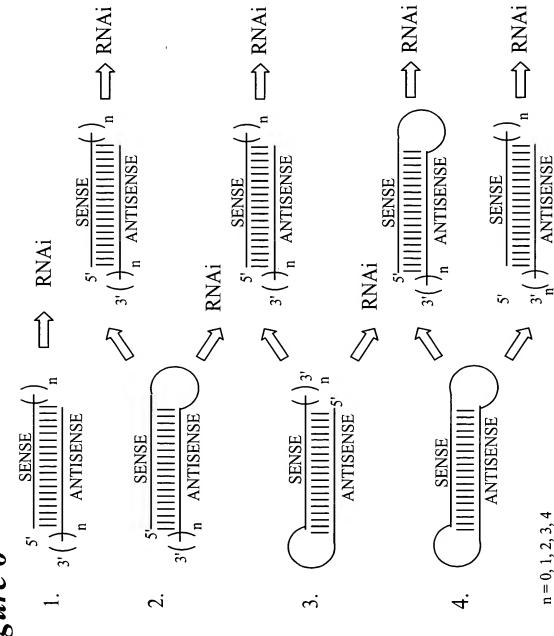
Figure 5

			_
A		SENSE STRAND (SEQ ID NO 465)	
	5'-	iB-UGUCUAUCAGCGCAGCUAC <i>TT</i> -iB	-3'
		L-T _S TACAGAUAGUCGCGUCGAUG	-5'
		ANTISENSE STRAND (SEQ ID NO 466)	
			J
	Ì	SENSE STRAND (SEQ ID NO 467)	ĺ
В	5'-	ugucu <u>a</u> uc <u>agcgcagcuacT_ST</u>	-3'
	√ 3'-	L-T _S T <u>acagauagucgcgucgaug</u>	-5' >
		ANTISENSE STRAND (SEQ ID NO 468)	_
			\langle
	[SENSE STRAND (SEQ ID NO 469)	
C	5'-	iB-u GucuAucAGcGcAGcuAcTT-iB	-3'
	₹ 3'-	L-T _S T A c A G A u A G u c G c G u c G A u G	-5' \
		ANTISENSE STRAND (SEQ ID NO 470)	
			$\stackrel{>}{\sim}$
		SENSE STRAND (SEQ ID NO 471)	
D	5'-	iB-u GucuAucAGcGcAGcuAcTT-iB	-3'
	3'-	$L-T_ST$ \underline{a} \underline{c} \underline{a} \underline{g} \underline{u} \underline{a} \underline{g} \underline{u} \underline{c} \underline{g} \underline{c} \underline{g} \underline{u} \underline{c} \underline{g} \underline{u} \underline{u} \underline{g}	-5'
		ANTISENSE STRAND (SEQ ID NO 468)	
	Ĺ	•	J
		SENSE STRAND (SEQ ID NO 472))
	5'-	iB-u G u c u A u c A G c G c A G c u A c T T-iB	-3'
${f E}$	₹ 3'-	L-T _S T _a c _a gauagucgcgucgaug	-5' >
		ANTISENSE STRAND (SEQ ID NO 468)	
	<u>C</u>	SENSE STRAND (SEQ ID NO 471)	\leq
		SENSE STRAND (SEQ ID NO 4/1)	
100	5'-	iB-u G u c u A u c A G c G c A G c u A c T T-iB	-3'
F	₹ 3'-	L-T _S T A c A G A u A G u c G c G u c G A u G	-5' >
		ANTISENSE STRAND (SEQ ID NO 473)	
			7

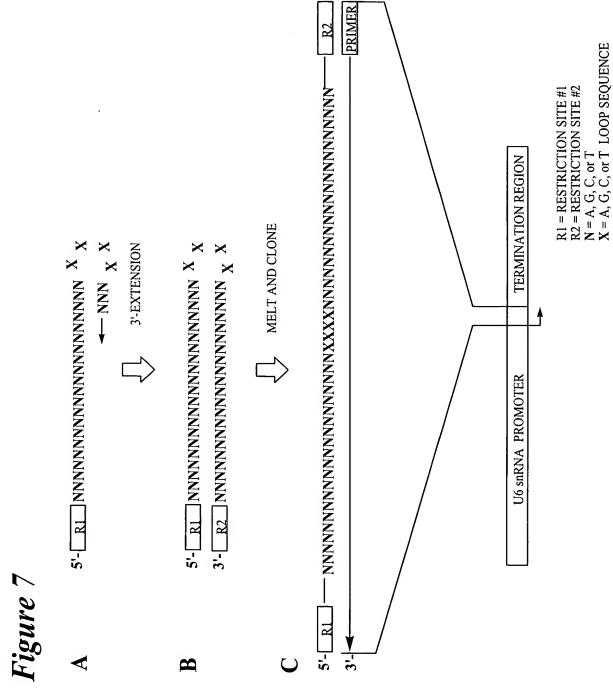
lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro $italic\ lower\ case = 2'-deoxy-2'-fluoro$ <u>underline</u> = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
iB = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY or iB OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE OPTIONALLY PRESENT





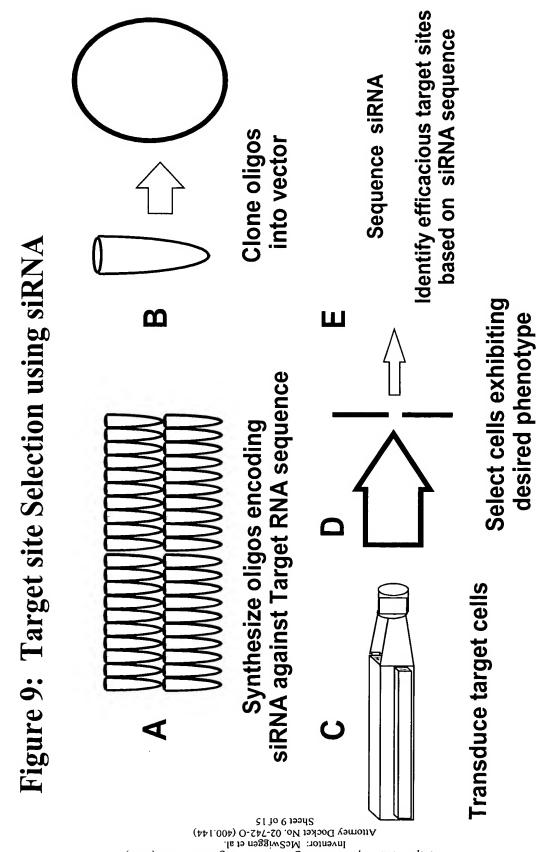
Receptor Gene Expression Using Short Interfering Mucleic Acid (siNA) Inventor: McSwiggen et al. Attorney Docket No. 02-742-O (400.144) Sheet 7 of 15

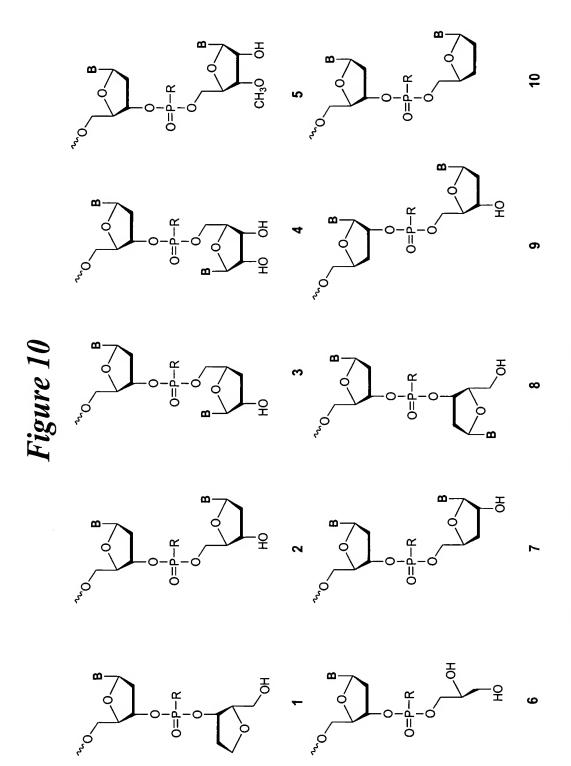


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R1 = RESTRICTION SITE #1 R2 = RESTRCTION SITE #2 N = A, G, C, or T X = A, G, C, or T CLEAVAGE WITH RESTRICTION U6 SnRNA PROMOTER **ENZYMES 1 AND 2** 3'-EXTENSION]NNNNNNNNNNNNNNNNNNNNNNNNN U6 snRNA PROMOTER

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R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

reporter system **Test for activity** in luciferase Figure 11: Modification Strategy activity vs unmodified Compare stability and Make an educated modification stability in human Test for nuclease serum

construct

Figure 12: Phosphorylated siNA constructs

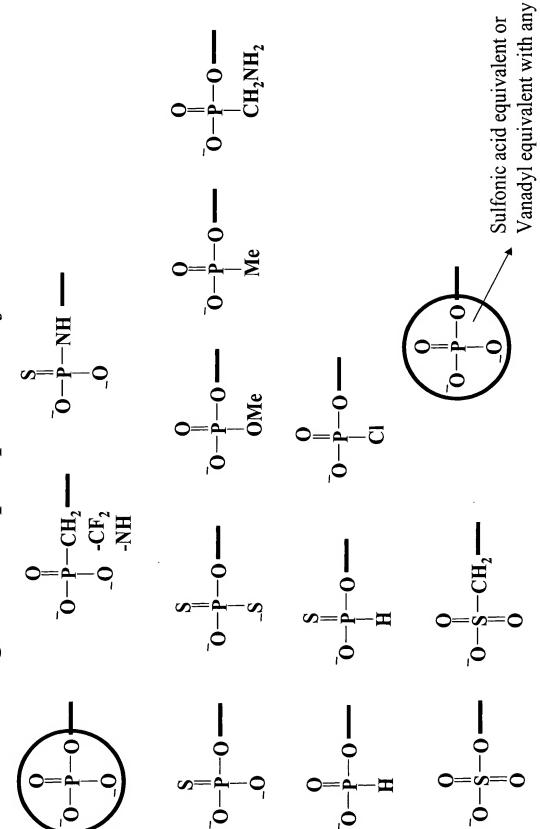
Asymmetric hairpin siNA

Asymmetric duplex siNA

 $\begin{array}{c}
0 \\
-o-p-o \\
-o
\end{array}$ (n) = number of base pairs (e.g. 3-18 bp)

: Expression Using Short interfering Muclei Inventor: McSwiggen et al. Attomey Docket No. 02-742-O (400.144) Sheet 12 of 15

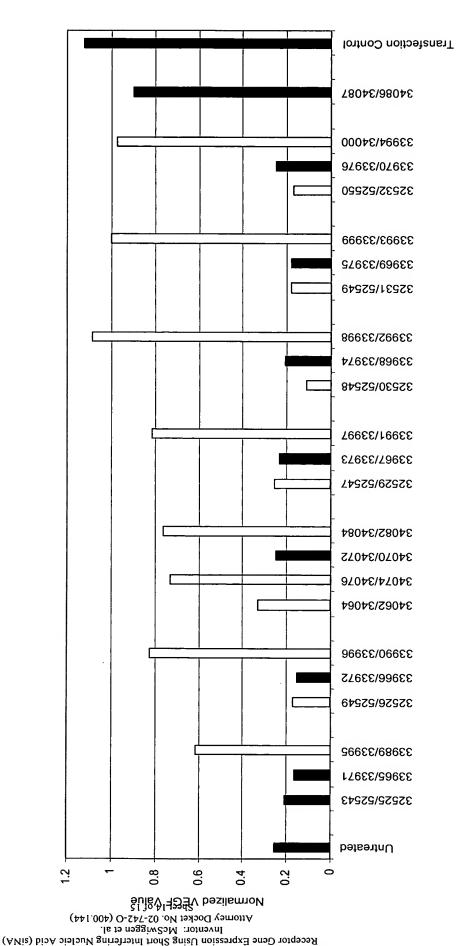
Figure 13: 5'-phosphate modifications



combination of other modifications herein

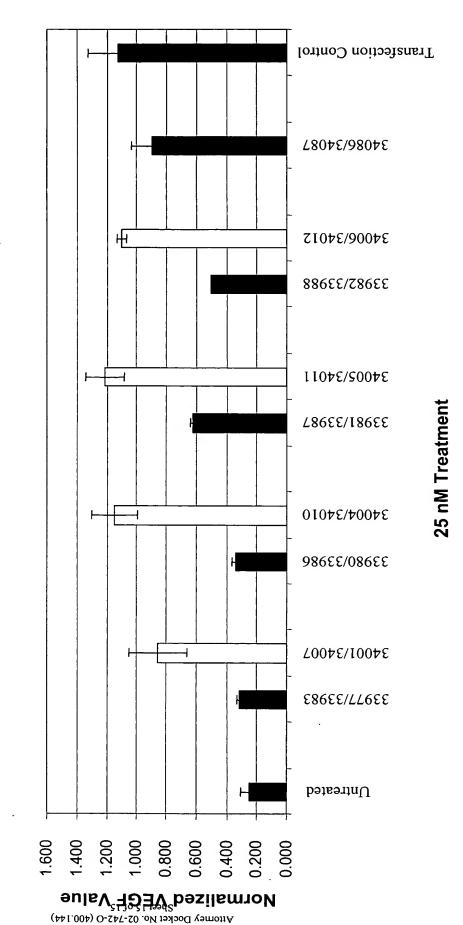
Title RMA Interference Mediated Inhibition of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor Gene Expression Using Short Interfering Mucleic Acid (siNA)
Inventor: McSwiggen et al.
Attorney Docket No. 02-742-O (400.144)
Sheet 13 of 15

Figure 14A: Inhibition of VEGF RNA expression using Stab 0/0 and Stab 9/10 siNA targeting VEGF RNA sequences



Title RNA Interference Mediated Inhibition of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor

Figure 14B: Inhibition of VEGF RNA expression using Stab 7/8 siNA targeting VEGF RNA sequences



Title RAA Interference Mediated Inhibition of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor
Receptor Gene Expression Using Short Interfering Nucleic Acid (siNA)
Inventor: McSwiggen et al.
Attorney Docket No. 03-743-0 (400, 144)